

## Appendix D. Excluded Studies

All studies listed below were reviewed in their full-text version and excluded for the reason shown in bold. Reasons for exclusion signify only the usefulness of the articles for this study and are not intended as criticisms of the articles.

### Abstract only or full text unobtainable

AlHilli MM, Dowdy SC, Weaver A, et al. Factors associated with synchronous ovarian and endometrial cancer: A population-based case control study. *Journal of Clinical Oncology*. 2011;29(15):2011-06..

Anonymous. The safety and contraceptive efficacy of a 24-day low-dose oral contraceptive regimen containing gestodene 60 microg and ethinylestradiol 15 microg. *Eur J Contracept Reprod Health Care*. 1999;4 Suppl 2(9-15. PMID: 14677620.

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Carney M, Goodman M, Lurie G, et al. NSAIDs do not prevent ovarian cancer. *Gynecologic Oncology*. 2012;125 SUPPL. 1:S97.

Cea-Soriano L, Blenk T, M-A AW, et al. Hormonal therapies and meningioma: A UK primary care study. *Pharmacoepidemiology and Drug Safety*. 2011;20 SUPPL. 1:S240-S241.

Coutinho Nunes F, Caetano C, Figueiredo Dias M, et al. Oral contraception and breast cancer. *European Journal of Contraception and Reproductive Health Care*. 2012;17 SUPPL. 1:S137.

Cramer DW, Titus-Ernstoff L and Vitonis AF. Genital talc use and ovarian cancer: Influence of histologic type and menopausal status on strength and dose response of the association. *Cancer Research*. 2011;71(8):2011-04.

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DeVries M, Agnihotram RV, Koushik A, et al. The role of environmental cofactors in the progression of cervical precancerous lesions. *American Journal of Epidemiology*. 2011;173 SUPPL. 11:S169.

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Dinger J, Bardenheuer K and Assmann A. Safety and effectiveness of oral contraceptives in obese women. *Pharmacoepidemiology and Drug Safety*. 2011;20 SUPPL. 1:S15-S16.

Dinger J, Bardenheuer K and Franke C. The risk of VTE in users of a 24-day regimen of a combined oral contraceptive compared to conventional 21-day OC regimens: Results from the INASOC study. *Pharmacoepidemiology and Drug Safety*. 2011;20 SUPPL. 1:S131.

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Feldman L, Goldstein L, Ouyang B, et al. Oral contraceptive and hormone replacement therapy in women with cerebral aneurysms. *Journal of NeuroInterventional Surgery*. 2010;2 SUPPL. 1:A13-A14.

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risk of gynecologic cancers. *Journal of Clinical Oncology*. 2011;29(15):2011-06.

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## **Nonrandomized study <100 subjects**

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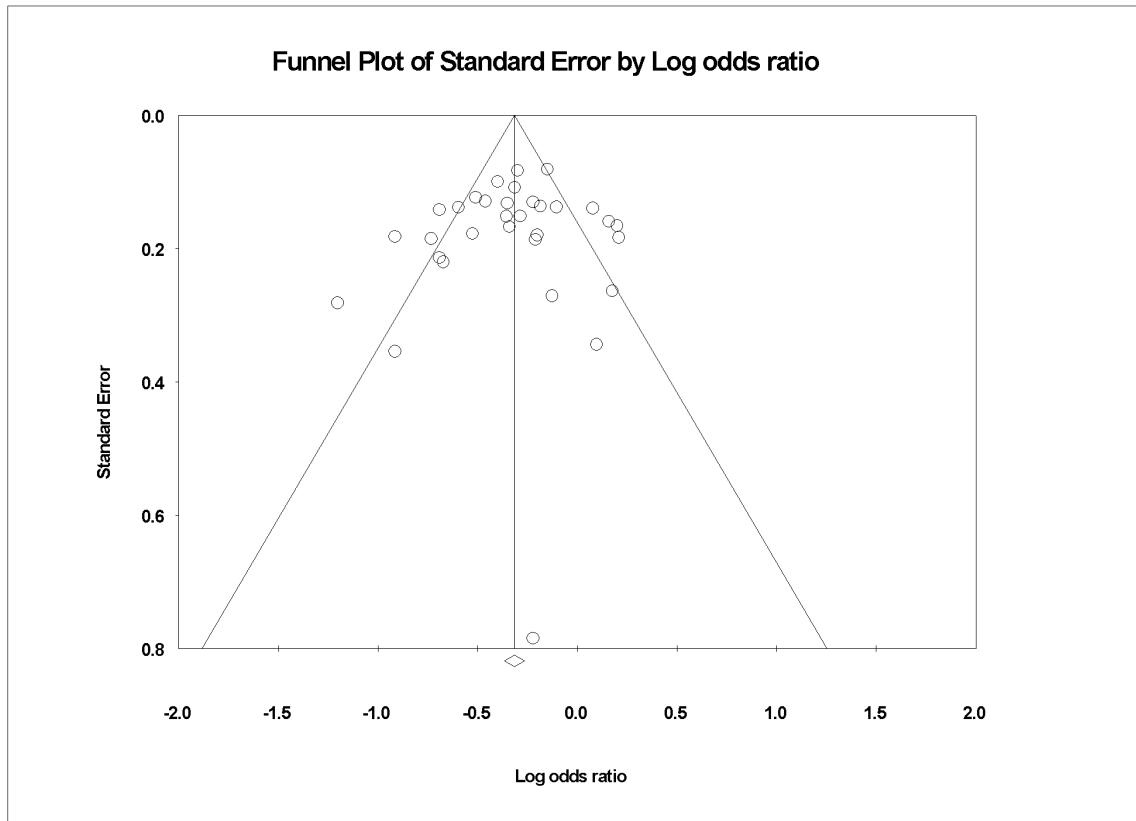
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## Appendix E. Analyses of Potential Publication Bias

We used Comprehensive Meta-Analysis Version 2 (Borenstein M, Hedges L, Higgins J, Rothstein H. Comprehensive Meta-analysis Version 2, Biostat, Englewood NJ [2005]) to test for potential publication bias for the outcomes described below. Figures E-1 to E-5 show the resulting funnel plot for each outcome. Note that there is no asymmetry in any of the plots.

### Ovarian Cancer Incidence

Figure E-1. Funnel plot for ovarian cancer incidence



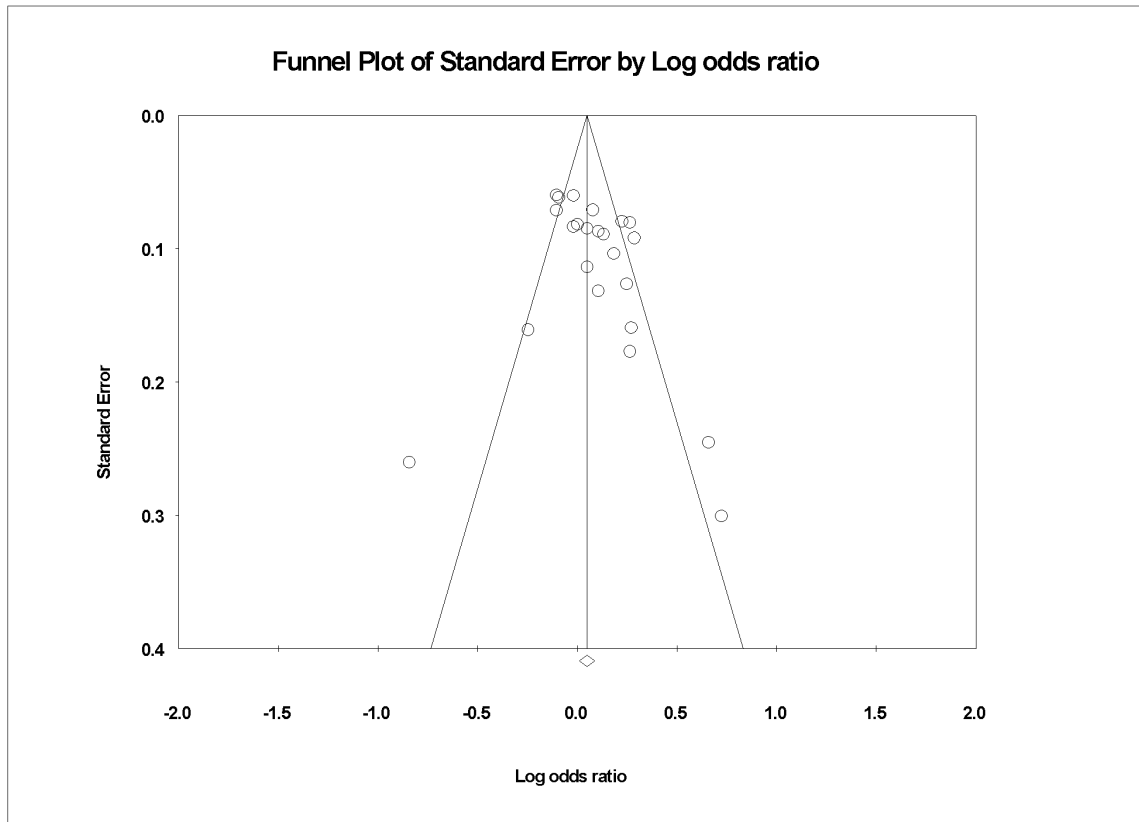
E-1

00803705



## Breast Cancer Incidence

Figure E-2. Funnel plot for breast cancer incidence

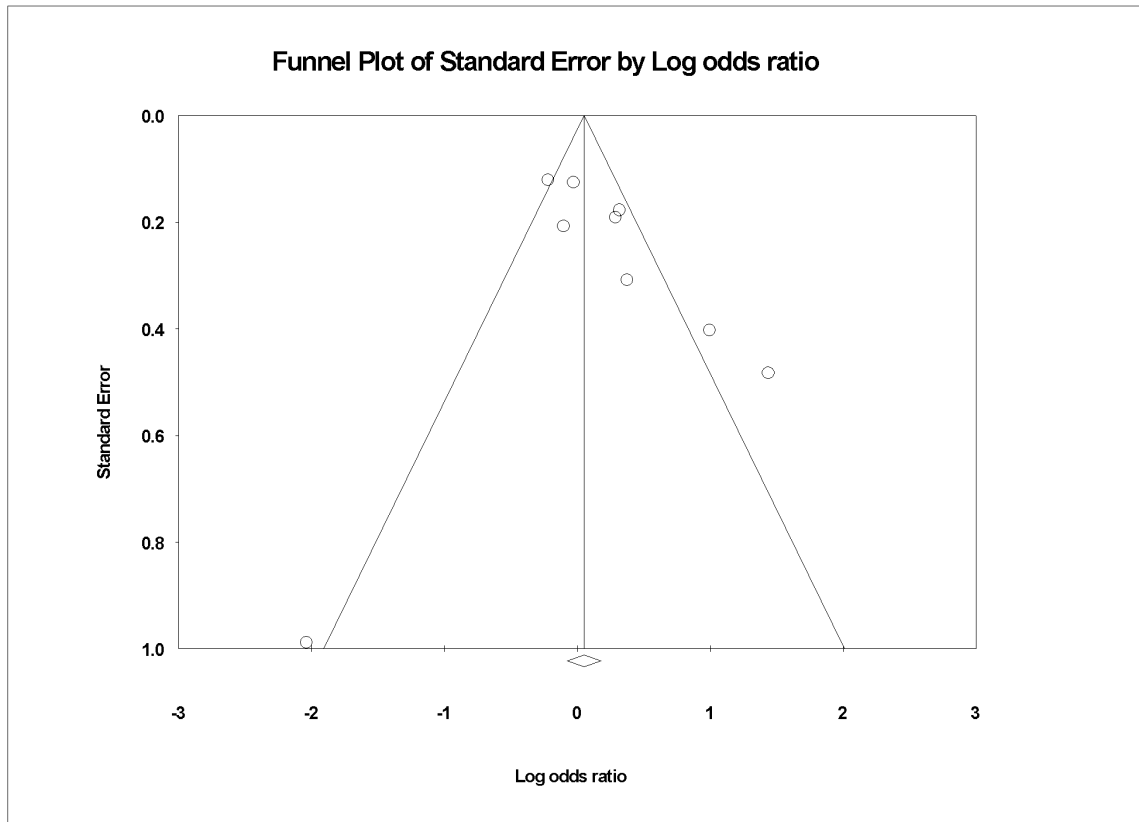


E-2

00803706

## Cervical Cancer Incidence

Figure E-3. Funnel plot for cervical cancer incidence

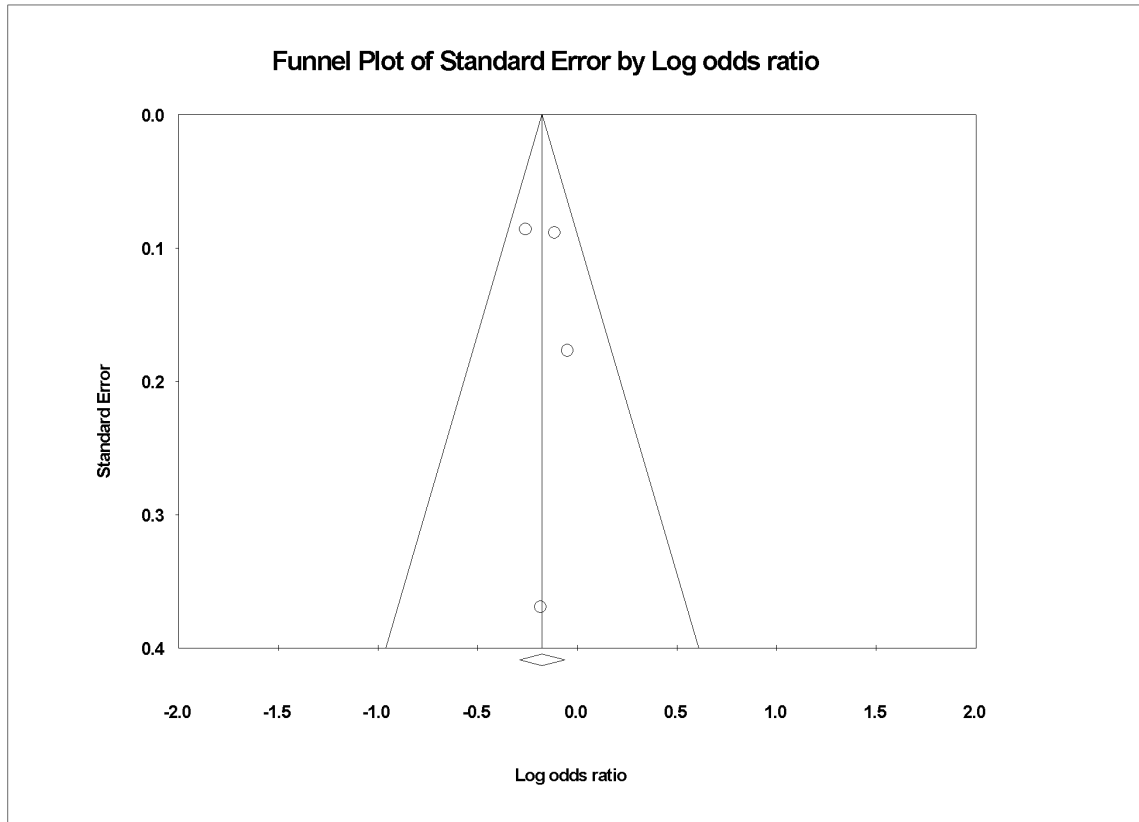


E-3

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## Colorectal Cancer Incidence

Figure E-4. Funnel plot for colorectal cancer incidence

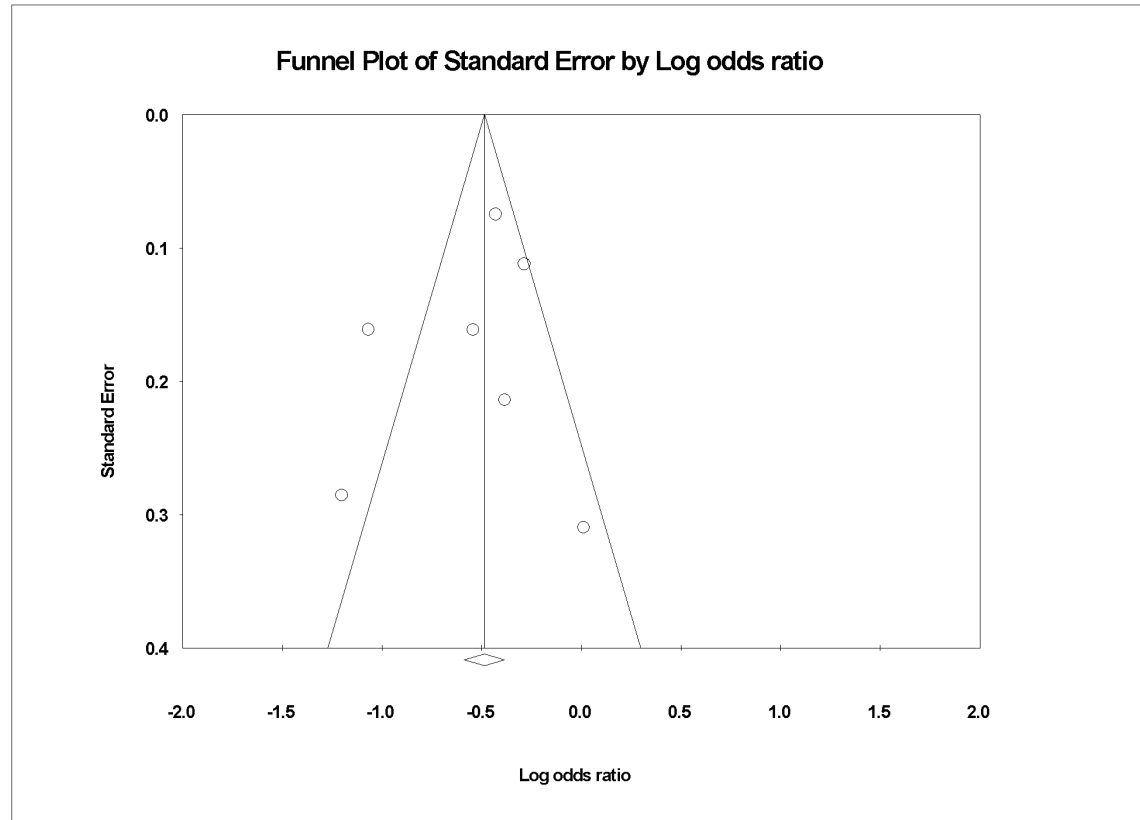


E-4

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## Endometrial Cancer Incidence

Figure E-5. Funnel plot for endometrial cancer incidence



We also computed Begg and Mazumdar's correlation test for publication bias for each cancer incidence (Table E-1). None of the correlations were significant although breast cancer incidence was marginal.

Table 1. Begg and Mazumdar's correlation test for publication bias

Cancer Incidence	Correlation	p-value
Ovarian	-0.055	0.6458
Breast	0.289	0.0539
Cervical	0.278	0.2972
Colorectal	0.000	1.0000
Endometrial	-0.048	0.8806

Overall, there was no evidence of publication bias in the meta-analyses.

## Appendix F. Model Description and Parameters

### General Considerations

We previously developed a simulation model for the natural history of ovarian cancer at the population level, which has provided insights into the potential effectiveness of screening as a strategy for reducing ovarian cancer morbidity and mortality,<sup>1,2</sup> and many of the basic parameters and model structure used in that model are used here. However, the ovarian cancer screening model—while including such relevant parameters as age-specific oophorectomy rates, age-specific ovarian cancer incidence, stage-specific survival, between-stage transition rates derived from the observed incidence and survival data, and the potential effect of known risk factors such as BRCA mutation status—focuses primarily on ovarian cancer mortality. For the purposes of quantifying the potential tradeoffs of benefits and harms for primary prevention of ovarian cancer through the use of oral contraceptives (OCs), there were three additional major considerations for the model:

1. The eight additional outcomes (breast, cervical, colorectal, endometrial cancers; and DVT, PE, MI, and stroke) needed to be included.
2. Specific characteristics of OC use, including ages at first and last use and duration of use, may affect the association between OCs and any of the relevant outcomes; so the model needed to incorporate a mechanism for including as many aspects of OC use as possible.
3. Many aspects of reproductive history—age at menarche, age at first pregnancy, numbers of pregnancies, breast feeding history, age at menarche, number of ovulatory cycles—are related to both OC use and the risk of ovarian cancer and many of the other outcomes of interest, either as confounders or effect modifiers. The balance of benefits and harms of OC use for primary prevention of ovarian cancer for specific women may well vary based on these other factors. Therefore, ultimately, a model that incorporates a mechanism for including relevant reproductive factors and their effect on ovarian cancer risk independent of OC use may prove quite useful (as well as have applications for other areas of reproductive health).

We initially developed a model that starts at age 10 and runs through age 100, and which includes age-specific and race/ethnicity-specific probabilities of menarche (including postmenarchal anovulatory cycles), age at sexual debut, contraceptive method prevalence, age-specific fecundity, contraceptive method-specific effectiveness, pregnancy (including age-specific miscarriage rates and race/ethnicity-specific probabilities of delivery by gestational age), lactation, and hysterectomy and oophorectomy rates as well as incidence and mortality from the nine conditions of interest. Although the model generated estimates of incidence and mortality that were consistent with observed data, we ultimately opted to simplify the reproductive components of the model for the following reasons:



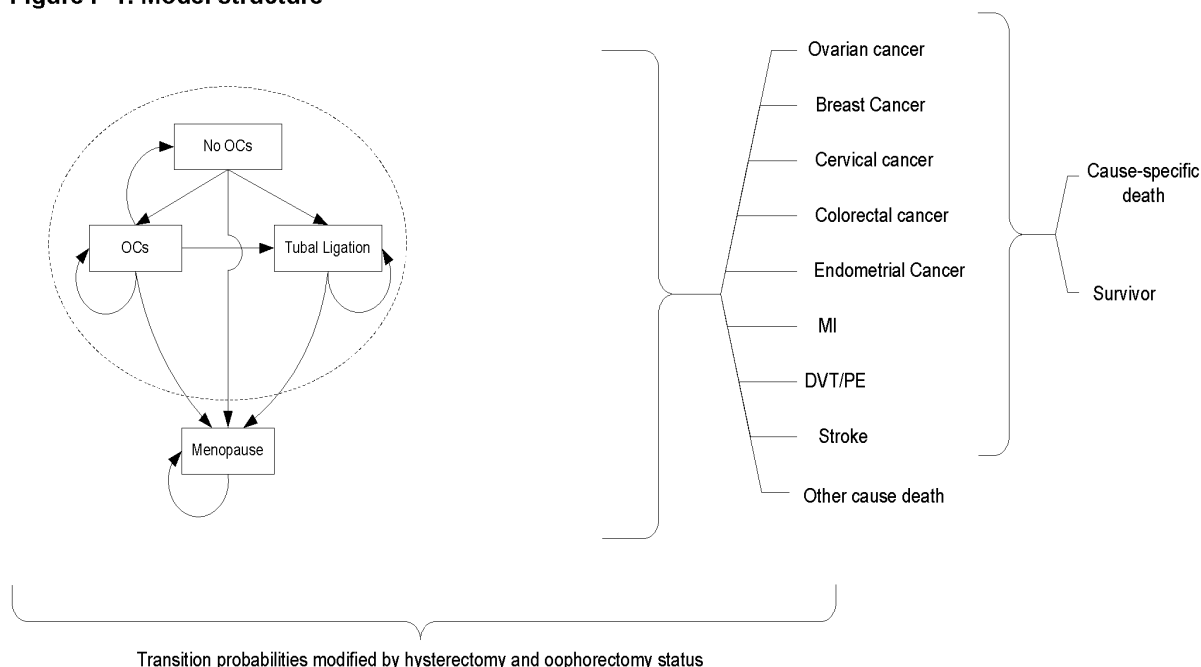
- The studies included in the meta-analyses almost always provided risk estimates for the association of OC use and outcomes, particularly for reproductive cancers that were adjusted for most, if not all, of the potentially relevant factors such as age at menarche and menopause. Without data on the separate parameter estimates (for example, the odds ratio for parity derived from a logistic regression model that also included OC use), modeling the joint effects was impossible.
- Even if these separate estimates were reported, there was wide disparity in how the parameters were described (categorical versus continuous, choice of categories, etc.), again making modeling difficult.
- The review of those studies which did assess joint effects of other reproductive factors did not detect significant differences.
- Although there are population-based data on the age-, race/ethnicity-, and parity-specific prevalence of the use of different contraceptive methods, as well as reasonable data on short-term method discontinuation rates, there are almost no data available for estimating the dynamics of contraceptive method switching. Because the only available data on duration of OC use did not provide data on patterns of intermittent use, we, like others, assumed that, once OC use began, women used it continuously for the specified duration (either assigned by the model or drawn from a distribution).
- Therefore,
  - We needed to assume continuous use of OCs.
  - The majority of the literature reviewed compared OC users with nonusers who used a mix of other available contraceptive methods (including no methods).
  - We found a paucity of data on the effect of contraceptive methods other than OCs and tubal ligation on ovarian cancer, our primary outcome of interest.
  - There were relatively small but noticeable effects of differential pregnancy rates (resulting from different contraceptive effectiveness) on outcome rates in early versions of the model, likely due to a competing risk effect; while further exploration of the implications of this effect of model structural assumptions on model output is definitely worthwhile, it was well outside the scope of work for this project.

We elected to simplify the model to just three “reproductive” states—OC users, OC nonusers, and tubal ligation for the purposes of this report. We plan further work on integrating a more detailed reproductive history into the model in future versions.

## Model Structure

The model is a semi-Markov state-transition model (Figure F-1); transition probabilities are conditioned on both the current state and time (i.e., age).

**Figure F-1. Model structure**



We have used Markov models extensively for analysis of clinical and policy decisions involving ovarian and cervical cancer, pregnancy, and other reproductive conditions, with transition probabilities modified by time (including age and time in state for cancer diagnoses) and current state. One limitation of the “standard” Markov model, particularly when run as a deterministic model, is the inability to readily modify transition probabilities based on past events (for example, number of prior pregnancies). Because the ability to modify the probability of the relevant outcomes based on past events is a critical requirement of the model, we used microsimulation, which allows further conditioning of transition probabilities on events prior to the current cycle.

## Software

The model was built in TreeAge Pro 2012 (Williamstown, MA: TreeAge, Inc.). Our decision to use TreeAge was based on our familiarity with it; most of our previous models were built using this program, which facilitated incorporating major portions of the relevant models. Iterative model building and modification, tree structure, updating parameters, using distributions, and model debugging are all relatively easy, and, given its widespread use among decision analysts, sharing of the model for purposes of review or collaboration is also straightforward. The major disadvantage of TreeAge is the relatively high computing resource requirements for complex stochastic simulations—some of the longer, more complex simulation

took more than 48 hours, even on a computer optimized for simulations. Given many of the uncertainties involved in this project, we prioritized flexibility in model building and revision over computational time. Ultimately, after a “final” structure has been identified, efficiency could be gained by recreating the model in a more efficient computing language.

## Simulation Method

The model is run as a microsimulation of U.S. females, starting at a uniform age of 10 and drawing from the current U.S. racial/ethnic distribution (defined as non-Hispanic white, African-American, Hispanic, and other). By performing a microsimulation, we can use TreeAge’s “tracker variable” capacity to allow the model to have “memory” of past events (e.g., time since last use of OCs, or age at menarche) in order to modify appropriate transition probabilities. Microsimulation also facilitates techniques such as value-of-information analysis for identifying future research priorities.

## Cycle Length

The model has cycles of 1 month duration, with all transition probabilities adjusted appropriately (e.g., annual cancer incidences are converted to monthly probabilities).

## Model States, Allowed Transitions, and Probabilities

Through the descriptions below, we refer to sources for parameter estimates, such as age- and race-specific rates, race-specific distributions of age, etc. In general, wherever possible, these data were used to define specific conditional probabilities based on age, race, or other relevant factors. For example, we used data on age- and race-specific prevalence of ever use of OCs to generate estimates of the monthly probability of starting OCs, given no prior use for each age and racial/ethnic category.

At the time of initial model building, the most recent available population data for many of our parameters at the time of initial model construction was from 2007. Unless otherwise noted, all values reflect estimates from that year. Subsequent versions of the model can be readily updated. When possible, we used point estimates and distributions defined by the data as described below.

The main report describes methods and sources for estimates of the relative risk of outcomes conditional on OC exposure, as well as the methods used to estimate incidence in exposed and unexposed women based on relative risk, prevalence of exposure, and overall incidence.

## Demographic Variables

**Race/ethnicity.** We used U.S. Census estimates of the 10- to 14-year-old female population in 2007 (<http://www.census.gov/popest/data/intercensal/national/nat2010.html>), divided into 4 mutually exclusive categories: non-Hispanic whites (56.9%), non-Hispanic blacks (14.9%), Hispanic (20.3%), and non-Hispanic other race (7.9%). Because the errors around these estimates are so small, we did not model these as distributions.

**General states:** For the purpose of estimating the overall balance of benefits and harms, nine health states potentially affected by OC use are included, in addition to other-cause mortality.

**Other-cause mortality.** During every cycle, individuals are at risk for age- and race-specific mortality for females. Once any of the potentially fatal states related to OCs become possible, other cause mortality is defined as age- and race-specific mortality for females minus cause-specific mortality for the five cancers, the four acute vascular events (DVT, PE, MI, and stroke), and pregnancy-related mortality.

Age-specific and race/ethnicity-specific all-cause mortality for females for 2007 was obtained from death certificate data maintained by the National Center for Health Statistics, accessed through the CDC's WONDER Web portal. We then subtracted the number of deaths attributed to malignancies of the ovary (C56), breast (C50), cervix (ICD-10 code C53), colon and rectum (C18-20), and uterine corpus (C54-55) as well as deep venous thrombosis (I82.8-I82.9), pulmonary embolism (I26), ischemic stroke (I63), and acute myocardial infarction (I21) from the total.

The monthly age- and race-specific probability of other cause mortality was then estimated by dividing the annual number of deaths in a given age/race/ethnicity stratum by the total number of women in that stratum in the Census data; this annual rate was then converted to a monthly probability by using the following formula:

$$Probability = 1 - e^{Rate * Time}$$

In order to facilitate simulations, we elected not to model these probabilities as a distribution for the purposes of the analyses presented here, but they could readily be transformed into beta distributions.

**Table F-1. Deaths from causes other than ovarian, breast, cervical, colorectal, or endometrial cancers, or deep venous thrombosis, pulmonary embolism, stroke, or acute myocardial infarction, by age and race/ethnicity, U.S. females, 2007**

Age Group	Race/Ethnicity			
	White	Black	Hispanic	Other
5-9	647	235	251	49
10-14	760	291	239	63
15-19	2404	630	485	163
20-24	2985	926	665	223
25-29	3315	1216	698	237
30-34	3744	1415	721	280
35-39	5845	2154	916	357
40-44	9954	3111	1175	548
45-49	16489	4772	1583	738
50-54	22347	6047	2003	885
55-59	29258	6469	2405	1198
60-64	39267	6051	2726	1376
65-69	48550	6658	3271	1649
70-74	66511	7427	4245	2076
75-79	102413	7466	5855	2764
80-84	149152	6942	7016	3460
85-89	174304	4268	6319	3184
90-94	137341	2321	4433	2294
95-99	61555	1623	2030	854



**Cancers: Ovarian, breast, cervical, colorectal, endometrial.** For each cancer, the probability of transitioning from one of the noncancer states is the age- and race-specific incidence for women (based on national registry data), adjusted for reproductive history and use of OCs using adjusted odds ratios and/or hazard ratios obtained from the literature review. Key assumptions include:

- For all nongynecologic cancers, we assume cancer incidences are independent and non-mutually exclusive—for example, an endometrial cancer survivor will still be at risk for breast cancer at the appropriate age- and race-specific value. Other than BRCA carriers, we assume that development of one type of cancer implies an increased risk for certain other types.
- We include only invasive cancers, not *in situ* or preinvasive lesions.
- We assume that definitive therapies for ovarian, cervical, and endometrial cancer eliminate the possibility of developing another cancer of the female genital tract.
- Cancer incidences are not adjusted for screening behaviors—SEER incidence statistics, for example, represent the weighted average of cancer incidence and stage distribution among screened and unscreened populations. Although reproductive history, including contraceptive use, may affect screening behavior, we did not attempt to adjust for this.
- Cancer survival reflects the weighted age- and race-specific stage distribution—we do not separate cancers by stage at this level of the simulation. Although incorporating stage distribution in subsequent versions of the model may have value for comparing the potential effects of primary prevention of ovarian cancer with OCs to screening, modeling stage-specific outcomes would increase the complexity of the model without providing significant benefit in terms of the primary questions of interest.
- We do not separate specific cancers by histologic subtype (e.g., epithelial versus germ cell tumors of the ovary, or squamous versus adenocarcinomas of the cervix).
- After cancer diagnosis, individuals are at risk for cancer-specific mortality for 5 years, then assumed to be cured, primarily because of variable data on longer term recurrence risk. This may underestimate lifetime mortality for some cancers, particularly breast cancer.

**Allowed transitions:** Cancer-specific death, cancer survivor, other cancers, other cause mortality, menopause

We obtained estimates of the age-specific (in 5-year age groups) incidence of ovarian, breast, cervical, colorectal, and endometrial cancers from two sources: (1) the Surveillance, Epidemiology, and End Results (SEER) database maintained by the National Cancer Institute (<http://seer.cancer.gov/canques/index.html>) and (2) the Centers for Disease Control and Prevention (CDC) National Program of Cancer Registries (<http://wonder.cdc.gov/wonder/help/cancernpcr-v2009.html>). Cancer incidence was modeled in a similar fashion to other cause mortality, using the estimated number of cases. We converted incidence (a rate), to probabilities as described above, and assumed that the pooled odds ratios from the meta-analyses were reasonable estimates of the relative risk. For cancer, we used these



numbers and the Census population estimates to beta distributions (which are bounded between 0 and 1) for probabilistic analyses.

**Table F-2. Number of ovarian cancers by age and race/ethnicity, United States, 2007**

Age Group	Race/Ethnicity			
	White	Black	Hispanic	Other
10-14	30	0	21	0
15-19	62	27	26	0
20-24	114	17	38	0
25-29	131	26	40	0
30-34	191	22	41	26
35-39	369	44	74	38
40-44	676	98	132	50
45-49	1263	139	156	82
50-54	1740	201	172	107
55-59	1948	188	200	81
60-64	2084	210	140	81
65-69	1885	196	135	51
70-74	1759	165	110	53
75-79	1716	148	107	31
80-85	1593	103	74	27
85+	1521	108	57	22

**Table F-3. Number of breast cancers by age and race/ethnicity, United States, 2007**

Age Group	Race/Ethnicity			
	White	Black	Hispanic	Other
10-14	0	0	0	0
15-19	0	0	0	0
20-24	83	38	32	0
25-29	514	160	125	0
30-34	1485	414	364	46
35-39	4072	994	760	171
40-44	9202	1843	1393	336
45-49	15407	2659	1788	714
50-54	17534	2965	1741	998
55-59	19690	2913	1576	973
60-64	20700	2536	1484	854
65-69	19000	2250	1285	688
70-74	16115	1776	960	497
75-79	15172	1387	764	355
80-85	12543	1072	513	264
85+	10698	874	360	156

**Table F-4. Number of cervical cancers by age and race/ethnicity, United States, 2007**

Age Group	Race/Ethnicity			
	White	Black	Hispanic	Other
10-14	0	0	0	0
15-19	0	16	0	0
20-24	81	66	26	0
25-29	326	145	103	0
30-34	597	170	197	21
35-39	952	225	295	72
40-44	999	265	294	51
45-49	1013	218	254	73
50-54	843	198	197	68
55-59	739	161	157	72
60-64	600	135	125	62
65-69	478	112	86	26
70-74	349	94	64	23
75-79	301	63	55	19
80-85	252	60	34	21
85+	219	0	24	0

**Table F-5. Number of colorectal cancers by age and race/ethnicity, United States, 2007**

Age Group	Race/Ethnicity			
	White	Black	Hispanic	Other
10-14	0	0	0	0
15-19	23	0	0	0
20-24	49	0	0	0
25-29	131	36	26	0
30-34	245	56	51	24
35-39	562	150	120	40
40-44	1213	312	177	67
45-49	2185	582	276	151
50-54	3498	943	452	261
55-59	4220	953	437	281
60-64	4901	888	447	254
65-69	5792	945	475	270
70-74	6504	1015	429	289
75-79	7935	950	504	286
80-85	8240	815	411	233
85+	9799	768	351	208

**Table F-6. Number of endometrial cancers by age and race/ethnicity, United States, 2007**

Age Group	Race/Ethnicity			
	White	Black	Hispanic	Other
10-14	0	0	0	0
15-19	0	0	0	0
20-24	0	0	0	0
25-29	73	17	55	0
30-34	224	42	92	24
35-39	539	64	151	46
40-44	1010	129	205	96
45-49	2107	219	211	149
50-54	3945	348	311	250
55-59	5401	555	399	236
60-64	5491	683	382	197
65-69	4273	649	294	135
70-74	3276	494	212	92
75-79	2762	352	141	75
80-85	2191	199	98	25
85+	1759	154	57	0

We converted incidence (a rate), to probabilities as described above, and assumed that the pooled odds ratios from the meta-analyses were reasonable estimates of the relative risk. We modeled the conditional probability of dying from each cancer for the first 5 years after diagnosis by using SEER relative survival data, stratified by age group and race. Survival data are stratified only as white versus black, without adjustment for ethnicity. We assumed that survival for Hispanics and non-Hispanic other races was identical to whites, and applied the estimates for blacks to non-Black Hispanics.

We used the number of cases at the start of the followup period and the reported relative survival rates for each year shown in the tables to generate estimates of the number of patients alive and dead at the start of each interval. These numbers were then used to create beta distributions for the annual probability of death, which were subsequently converted to monthly probabilities.

**Table F-7. 5-year relative survival by age and race for ovarian cancer**

Race and Age	Percent Surviving at End of Interval					
White						
Age	Number at Start of Followup	1 year	2 years	3 years	4 years	5 years
0-44	1106	93.90%	87.80%	83.30%	79.50%	74.40%
45-45	1805	91.00%	80.80%	71.60%	65.00%	59.20%
55-64	2197	86.10%	73.70%	61.70%	52.50%	46.10%
65-74	1829	76.00%	60.90%	50.40%	41.70%	34.00%
75+	2568	1.00%	1.20%	1.30%	1.40%	1.50%
Black						
Age						
0-44	171	50.80%	38.70%	31.60%	25.60%	21.70%
45-45	195	87.20%	77.70%	69.70%	66.30%	62.90%
55-64	207	76.90%	62.80%	52.60%	44.70%	38.60%
65-74	174	67.90%	55.70%	41.20%	38.20%	33.10%
75+	169	40.80%	30.40%	22.20%	15.20%	14.40%

**Table F-8. 5-year relative survival by age and race for breast cancer**

Race and Age	Percent Surviving at End of Interval					
White						
Age	Number at Start of Followup	1 year	2 years	3 years	4 years	5 years
0-44	11,155	99.00%	96.40%	94.10%	91.90%	89.60%
45-45	21,053	99.00%	97.20%	95.20%	93.60%	92.20%
55-64	21,814	98.30%	96.70%	95.00%	93.40%	91.90%
65-74	16,933	98.10%	96.90%	95.10%	93.40%	92.20%
75+	18,574	0.10%	0.20%	0.30%	0.30%	0.40%
Black						
Age						
0-44	2090	96.40%	94.40%	92.90%	91.90%	90.50%
45-45	2943	96.70%	90.00%	83.90%	79.70%	75.90%
55-64	2476	96.60%	90.20%	85.10%	81.10%	77.90%
65-74	1599	95.50%	91.00%	87.00%	82.60%	79.60%
75+	1411	88.40%	83.80%	80.10%	74.50%	72.30%

**Table F-9. 5-year relative survival by age and race for cervical cancer**

Race and Age		Percent Surviving at End of Interval				
<i>White</i>						
<i>Age</i>	Number at Start of Follow-up	1 year	2 years	3 years	4 years	5 years
0-44	2,160	95.90%	90.00%	87.00%	85.60%	84.80%
45-45	1,059	88.40%	79.10%	73.70%	70.10%	66.30%
55-64	686	83.10%	71.40%	66.80%	63.90%	61.00%
65-74	456	77.60%	69.50%	61.60%	57.80%	53.30%
75+	378	2.00%	2.30%	2.60%	2.70%	3.00%
<i>Black</i>						
<i>Age</i>						
0-44	369	59.00%	45.50%	41.00%	36.00%	30.30%
45-45	218	90.30%	79.70%	75.70%	74.10%	73.30%
55-64	171	85.70%	75.90%	71.60%	65.30%	60.00%
65-74	105	82.10%	71.00%	67.80%	62.50%	59.40%
75+	94	60.00%	43.90%	42.00%	35.60%	28.70%

**Table F-10. 5-year relative survival by age and race for colorectal cancer**

Race and Age		Percent Surviving at End of Interval				
<i>White</i>						
<i>Age</i>	Number at Start of Followup	1 year	2 years	3 years	4 years	5 years
0-44	1,384	93.10%	85.60%	79.30%	75.70%	72.50%
45-45	3,150	92.70%	85.80%	80.90%	76.40%	73.70%
55-64	4,574	90.00%	82.40%	77.30%	73.50%	70.40%
65-74	6,334	85.40%	78.80%	74.30%	71.10%	68.90%
75+	13,107	0.50%	0.60%	0.60%	0.70%	0.80%
<i>Black</i>						
<i>Age</i>						
0-44	323	74.90%	68.50%	64.60%	62.70%	61.30%
45-45	764	89.00%	76.20%	69.00%	63.80%	63.20%
55-64	952	88.30%	79.90%	73.60%	68.60%	65.70%
65-74	948	85.00%	74.90%	68.80%	65.10%	61.30%
75+	1246	67.10%	58.50%	52.60%	50.00%	46.80%



**Table F-11. 5-year relative survival by age and race for endometrial cancer**

Race and Age	Percent Surviving at End of Interval					
	Number at Start of Followup	1 year	2 years	3 years	4 years	5 years
<i>White</i>						
Age						
0-44	1,271	97.60%	94.90%	93.80%	92.40%	91.70%
45-45	3,571	96.40%	94.40%	92.50%	91.40%	90.10%
55-64	5,719	96.10%	93.30%	91.00%	89.50%	89.10%
65-74	4,007	94.00%	89.70%	87.20%	85.60%	83.90%
75+	3,606	0.40%	0.60%	0.70%	0.70%	0.90%
<i>Black</i>						
Age						
0-44	226	86.80%	80.70%	76.90%	74.70%	73.90%
45-45	309	90.40%	84.30%	80.00%	76.20%	74.70%
55-64	538	84.90%	76.50%	69.90%	67.30%	66.50%
65-74	470	86.50%	75.70%	71.00%	64.70%	63.40%
75+	269	70.50%	58.40%	49.80%	49.00%	46.40%

**Vascular events: Deep venous thrombosis, pulmonary embolus, stroke, myocardial infarction.** As with cancer, age- and race-specific incidences for these states are adjusted for OC use status as described below. Other key assumptions:

- Women who experience one of these events while on OCs will not use OCs afterwards.
- For women under the age of 65, the best population-level data for estimating both incidence and mortality is hospital discharge data. This may underestimate incidence by missing cases that are diagnosed and managed completely as outpatients, and underestimate mortality by missing postdischarge deaths.

**Allowed transitions:** Condition-specific mortality, survivor, cancers, other acute complications

Estimates of admissions for women by age and race/ethnicity were generated using the Nationwide Inpatient Sample (NIS) dataset from 2000 to 2007, a publicly available survey of a mix of community hospital inpatient settings that surveys diagnoses, procedures, length of stay, and costs associated with approximately 20 percent of all U.S. inpatient discharges (<http://www.hcup-us.ahrq.gov/nisoverview.jsp>).

Discharges within the NIS data were used to estimate national numbers of admissions for the vascular events of interest, using ICD-9 diagnosis codes, specifically acute myocardial infarction (410.x), pulmonary embolus (415.1), stroke (430.x, 431.x, 432.x, 434.x) and DVT (453.x). Estimates were weighted using available survey weights and subset into mutually exclusive categories comprised of 5-year age groups (15–85+) and race/ethnicity categories (white, black, Hispanic, other).

Hospital admission probabilities were estimated by using the point estimate and standard errors to generate gamma distributions (bounded by 0 at the lower end) for the annual number of admissions. During the simulations, the probability was calculated by drawing a number from the gamma distribution, dividing this number by the total number of women in a given age and race/ethnicity stratum and converting the rate to a probability.

We present only point estimates here—the standard errors used to generate the gamma distributions are available from the authors.

**Table F-12. Annual admissions for deep venous thrombosis by age and race/ethnicity for U.S. females**

Age Group	Race/Ethnicity			
	White	Black	Hispanic	Other
15-19	678	210	125	25
20-24	1320	577	253	70
25-29	1813	928	499	198
30-34	2359	1292	617	215
35-39	3159	1687	747	250
40-44	4914	2529	874	339
45-49	6373	2955	1086	486
50-54	7330	2794	1132	630
55-59	8443	3008	1280	704
60-64	10024	3167	1225	692
65-69	11163	3127	1350	817
70-74	13111	3560	1405	964
75-79	16762	3206	1603	937
80-85	18656	2918	1444	1106
85+	24442	3645	1658	1218

**Table F-13. Annual admissions for pulmonary embolism by age and race/ethnicity for U.S. females**

Age Group	Race/Ethnicity			
	White	Black	Hispanic	Other
15-19	448	127	56	35
20-24	1020	417	148	45
25-29	1315	622	226	86
30-34	1758	840	233	183
35-39	1957	1296	329	143
40-44	3014	1472	484	225
45-49	4150	1476	486	268
50-54	4804	1394	449	299
55-59	5688	1458	479	393
60-64	6406	1340	522	345
65-69	7582	1631	576	437
70-74	8532	1782	616	394
75-79	10044	1655	646	490
80-85	9954	1338	594	475
85+	10793	1368	624	349

**Table F-14. Annual admissions for stroke by age and race/ethnicity for U.S. females**

Age Group	Race/Ethnicity			
	White	Black	Hispanic	Other
15-19	158	104	76	37
20-24	211	112	121	71
25-29	302	180	126	53
30-34	555	312	209	144
35-39	831	446	279	180
40-44	1906	765	389	301
45-49	3348	1398	643	358
50-54	5930	2035	909	555
55-59	8452	1878	1054	790
60-64	13234	1986	1402	910
65-69	17362	2699	1419	1199
70-74	21758	2468	1903	1542
75-79	27856	2821	1796	1708
80-85	29142	2384	1423	1572
85+	31688	2416	1247	1725

**Table F-15. Annual admissions for acute myocardial infarction by age and race/ethnicity for U.S. females**

Age Group	Race/Ethnicity			
	White	Black	Hispanic	Other
15-19	37	5	3	0
20-24	120	64	42	10
25-29	259	204	57	15
30-34	606	446	132	58
35-39	1472	567	194	134
40-44	3297	1169	524	389
45-49	6388	2155	872	617
50-54	9631	3034	1280	912
55-59	13318	3374	1774	1243
60-64	18156	3552	1979	1329
65-69	20389	3720	2310	1985
70-74	24600	4162	2365	1973
75-79	31846	4013	2733	2298
80-85	37194	3768	2392	2480
85+	58620	4883	2690	3046

Mortality for each event was estimated using the number of patients in a given age/race stratum in the NIS with each diagnosis who had a discharge status of “death,” together with the total number of admissions within a given diagnosis/age/race stratum, to generate beta distributions for the conditional probability of death given the occurrence of the event. We assumed all deaths occurred during the same cycle as the event.

**Table F-16. Annual deaths during hospitalization for deep venous thrombosis by age and race/ethnicity for U.S. females**

Age Group	Race/Ethnicity			
	White	Black	Hispanic	Other
15-19	8	3	0	0
20-24	10	5	9	5
25-29	21	11	10	0
30-34	47	9	19	10
35-39	54	44	47	10
40-44	92	45	18	10
45-49	140	120	42	20
50-54	296	111	50	48
55-59	405	139	72	36
60-64	444	194	79	55
65-69	629	156	54	63
70-74	816	212	64	76
75-79	1136	186	145	57
80-85	1081	194	96	117
85+	1686	297	139	77

**Table F-17. Annual deaths during hospitalization for pulmonary embolism by age and race/ethnicity for U.S. females**

Age Group	Race/Ethnicity			
	White	Black	Hispanic	Other
15-19	5	0	0	5
20-24	20	14	9	0
25-29	15	16	10	5
30-34	26	10	14	10
35-39	30	61	21	5
40-44	87	69	44	5
45-49	145	119	30	10
50-54	354	106	13	37
55-59	347	115	45	26
60-64	521	170	89	43
65-69	618	114	33	55
70-74	723	158	50	30
75-79	811	140	88	56
80-85	907	105	42	50
85+	1225	176	85	59

**Table F-18. Annual deaths during hospitalization for stroke by age and race/ethnicity for U.S. females**

Age Group	Race/Ethnicity			
	White	Black	Hispanic	Other
15-19	39	15	0	0
20-24	14	10	14	15
25-29	38	25	5	8
30-34	34	55	24	0
35-39	154	77	37	9
40-44	216	137	47	42
45-49	285	177	81	48
50-54	474	250	133	66
55-59	539	203	123	96
60-64	683	172	110	131
65-69	793	274	99	87
70-74	1148	177	171	160
75-79	1491	292	165	201
80-85	2096	232	143	185
85+	2992	329	175	221

**Table F-19. Annual deaths during hospitalization for myocardial infarction by age and race/ethnicity for U.S. females**

Age Group	Race/Ethnicity			
	White	Black	Hispanic	Other
15-19	13	0	0	0
20-24	10	5	0	4
25-29	15	10	9	0
30-34	31	24	19	0
35-39	69	57	5	10
40-44	132	76	32	6
45-49	244	155	51	36
50-54	519	166	60	44
55-59	834	232	169	71
60-64	1235	334	164	84
65-69	1574	378	179	167
70-74	2359	410	203	246
75-79	3595	447	337	289
80-85	4892	504	391	328
85+	9507	803	502	463

**Surgical removal of pelvic organs—hysterectomy and/or oophorectomy.** Removal of the organ at risk eliminates the probability of developing cancer in that organ, and there is some evidence that removal of the uterus reduces ovarian cancer risk even if the ovaries are preserved. Because hysterectomy is performed for a variety of indications, often with removal of the ovaries, and is quite common in the U.S. (with up to 30% of women undergoing hysterectomy by age 65), we incorporated age- and race-specific hysterectomy and oophorectomy rates for



conditions other than cancers of the pelvic organs into the model, and adjusted probabilities for cancer development accordingly. We assumed the following:

- The probability of hysterectomy and/or oophorectomy is independent of OC use. Because OCs may reduce the risk of some conditions such as endometriosis which are common indications for hysterectomy, this may not be the case.
- These procedures are increasing being done on an outpatient basis; relying on discharge data may underestimate the rates.

Estimates were again derived from the NIS, excluding women with a diagnosis of any cancer of the cervix (180.x), uterus (182.x), or ovary (183.x). ICD-9 procedural codes were used to identify hysterectomy alone (68.4x, 68.5x, 68.9x), and with either bilateral (65.5x, 65.6x) or unilateral (65.3x, 65.4x) oophorectomy. Unilateral and bilateral oophorectomy without hysterectomy were also included. As with vascular event hospitalizations, we used point estimates and standard errors to generate gamma distributions, which in turn provided the numerator for estimating age- and race/ethnicity-specific probabilities.

**Table F-20. Annual hospitalizations for hysterectomy alone by age and race/ethnicity for U.S. females**

Age Group	Race/Ethnicity			
	White	Black	Hispanic	Other
15-19	25	6	24	0
20-24	714	108	122	49
25-29	4002	634	482	146
30-34	8491	1902	1702	621
35-39	15776	4940	3920	1177
40-44	20735	7021	5494	2251
45-49	15636	4261	3401	1645
50-54	6093	970	1074	514
55-59	3002	198	534	205
60-64	2718	149	367	217
65-69	2545	108	413	198
70-74	2056	104	239	185
75-79	1753	52	152	85
80-85	864	11	64	40
85+	206	37	4	4

**Table F-21. Annual hospitalizations for hysterectomy with unilateral oophorectomy by age and race/ethnicity for U.S. females**

Age Group	Race/Ethnicity			
	White	Black	Hispanic	Other
15-19	5	0	6	0
20-24	149	10	5	11
25-29	743	86	68	44
30-34	1786	373	245	90
35-39	3235	951	704	250
40-44	4616	1448	956	353
45-49	3749	1137	760	460
50-54	1332	308	200	126
55-59	489	84	76	59
60-64	391	25	56	22
65-69	286	15	38	48
70-74	285	10	18	9
75-79	112	11	38	11
80-85	108	0	9	8
85+	30	0	5	0

**Table F-22. Annual hospitalizations for hysterectomy with bilateral oophorectomy by age and race/ethnicity for U.S. females**

Age Group	Race/Ethnicity			
	White	Black	Hispanic	Other
15-19	23	0	5	0
20-24	271	24	16	9
25-29	1735	175	121	98
30-34	4125	494	316	190
35-39	7284	1208	813	465
40-44	15616	2885	2084	1200
45-49	24673	5260	3907	2450
50-54	17672	3307	2420	1760
55-59	8733	1052	1089	739
60-64	5847	723	705	413
65-69	4438	402	519	344
70-74	2644	244	317	238
75-79	1859	142	196	180
80-85	993	63	49	46
85+	507	52	43	14

**Table F-23. Annual hospitalizations for unilateral oophorectomy alone by age and race/ethnicity for U.S. females**

Age Group	Race/Ethnicity			
	White	Black	Hispanic	Other
15-19	5463	1904	1950	687
20-24	10375	3427	3351	1243
25-29	17637	5439	4719	2273
30-34	25214	7276	6309	3143
35-39	32831	9368	6856	3604
40-44	34752	9753	6658	4054
45-49	25178	6270	4215	2605
50-54	12685	2130	1465	1070
55-59	8212	1123	788	456
60-64	6798	879	659	293
65-69	6914	638	618	384
70-74	7135	593	470	341
75-79	6949	560	382	288
80-85	5161	291	235	150
85+	3865	193	155	118

**Table F-24. Annual hospitalizations for bilateral oophorectomy alone by age and race/ethnicity for U.S. females**

Age Group	Race/Ethnicity			
	White	Black	Hispanic	Other
15-19	149	34	49	24
20-24	859	140	151	71
25-29	3819	645	483	204
30-34	9314	2026	1179	536
35-39	17836	4083	2461	1165
40-44	31852	7904	4411	2315
45-49	43168	9786	5895	4124
50-54	33232	5858	3512	2399
55-59	21266	2267	1717	1327
60-64	17005	1460	1258	819
65-69	15796	1270	1117	711
70-74	13198	672	808	639
75-79	10171	463	548	465
80-85	5990	286	283	194
85+	3048	104	126	163

## Reproductive States

**Menopause.** We used published data to generate conditional probabilities of natural menopause by age.<sup>3</sup> Although the paper by Gold et al. found some differences in menopause probabilities by race and ethnicity, hazard ratios included 1, and we elected to model only age-specific probabilities. We assumed that women undergoing bilateral oophorectomy with or without hysterectomy, as well as women receiving definitive treatment for gynecologic cancers, were menopausal. We did not adjust menopausal probabilities in women who had undergone hysterectomy with ovarian preservation. We assumed that no woman underwent nonsurgical menopause prior to age 41, and all women had undergone menopause by age 55.

**Table F-25. Conditional probability of natural menopause by age**

Age	Conditional Probability
15-40	0.00%
41	1.02%
42	1.03%
43	1.04%
44	1.05%
45	2.15%
46	4.49%
47	4.71%
48	11.84%
49	11.76%
50	23.64%
51	37.50%
52	60.00%
53	66.67%
54	100.00%

**Allowed transitions:** Other cause mortality, cancers, acute complications

**Probability of contraceptive use.** Estimates of contraception use were generated using the National Survey of Family Growth (NSFG) 2002 and 2006 to 2010 data sets. The NSFG is a survey conducted by the Centers for Disease control that gathers information on family life, marriage and divorce, pregnancy, infertility, use of contraception, and men's and women's health (<http://www.cdc.gov/nchs/nsfg.htm>), and supplemented with the literature as needed.

Estimates of national female contraception prevalence rates and accompanying standard deviations were generated using the NSFG dataset. All estimates were subset by age, race, and prior pregnancy/birth status distribution and were weighted to generate national-level estimates. Survey data was limited to women aged 15 to 44 and excluded women pregnant at the time of the survey. All other women were included. Total survey weights reflected 59 million women aged 15 to 44. Subset analysis was performed by creating several mutually exclusive categories. Age was analyzed by categorizing patients into 5-year age groups (6 groups total); race/ethnicity as white, black, Hispanic, or other; and prior birth and pregnancy status as never pregnant, pregnant with no live births, one live birth, two live births, or more than two live births. For each of these groups, estimates were for the following contraception categories:

1. Female sterilization
2. Male sterilization
3. OCs
4. Other hormonal methods (Norplant or Implanon implant, Lunelle (injectable), Depo-Provera (injectable), contraceptive patch, contraceptive ring, morning-after pill)
5. IUD
6. Barrier methods (diaphragm with or without jelly or cream, male condom, foam, Today sponge, suppository or insert, jelly or cream without diaphragm)
7. Periodic abstinence (NFP, cervical mucus test or temperature rhythm, calendar rhythm)
8. No method (withdrawal, other method, other nonuser—had intercourse in the 3 months prior to interview)
9. Not sexually active (other nonuser—never had intercourse since first period, other nonuser—has had intercourse but not in the 3 months prior to interview)
10. Other not at risk (pregnant; seeking pregnancy; postpartum; sterile-nonsurgical, female; sterile-nonsurgical, male; sterile-surgical, female noncontraceptive; sterile-surgical, male noncontraceptive; sterile-unknown reasons, male)

For the purposes of this analysis, we categorized contraceptive methods as oral contraceptives, female sterilization, and all others (including nonuse).



**Age at first use of OCs.** We used age-specific prevalences from the NSFG to generate conditional probabilities of use by age and race/ethnicity.

**Table F-26. Conditional probability of oral contraceptive use by age and race/ethnicity**

Age Group	Race/Ethnicity			
	White	Black	Hispanic	Other
10-14	11.45%	21.82%	5.62%	5.62%
15-19	24.03%	14.37%	12.98%	29.06%
20-24	50.29%	29.86%	46.91%	28.05%
25-29	37.40%	32.34%	22.38%	34.04%
30-34	22.63%	5.58%	22.98%	21.31%
35-39	4.88%	12.80%	14.75%	37.19%
40	0	0	0	0

**Duration of use.** We found only one study which provided data to generate distributions for duration of use,<sup>4</sup> which reported a mean of 54.8 months with a standard deviation of 41 months. We used these to generate a gamma distribution, with a range of 1-308 months, 10<sup>th</sup> percentile of 13 months, 50<sup>th</sup> percentile of 45 months, and 90<sup>th</sup> percentile of 110 months.

**Age-specific probability of tubal ligation.** We used published estimates of the number of procedures by age and race/ethnicity, along with the total number of women in each stratum, to generate beta distributions for the probability of tubal ligation.

**Table F-27. Conditional probability of oral contraceptive use by age and race/ethnicity**

Age Group	Race/Ethnicity			
	White	Black	Hispanic	Other
15-19	0	0	3083	3591
20-24	74769	40201	29260	22458
25-29	670855	155335	125356	66347
30-34	408671	223174	346754	102707
35-39	401060	114853	139134	655
40-44	486188	255996	273579	87172

## Model Predictions Compared With SEER Estimates

Table F-28 compares mean predicted lifetime cancer incidence and mortality from age 10 to 100 for a 60,000-iteration simulation of our “base-case” model, where the effects of OC use on age- and race-specific incidence are modeled based on “ever/never” status and population-level estimates of patterns of OC use, and cancer-specific mortality is modeled as age- and race-specific post-diagnosis survival, to estimates for lifetime incidence and mortality from age 10 through 100 derived from the SEER DevCan Program (<http://surveillance.cancer.gov/devcan/>). DevCan models overall incidence using the same SEER datasets used for the model, but mortality estimates are independently derived based on death certificate data reported to the National Center for Health Statistics.

**Table F-28. Model predictions compared with SEER estimates**

Cancer Type	Lifetime Incidence		Lifetime Mortality	
	SEER DevCan	Model	SEER DevCan (Death Certificate)	Model (Incidence-based)
Ovarian cancer	1.37%	1.40%	1.98%	0.78%
Breast cancer	12.51%	11.0%	2.8%	0.98%
Cervical cancer	0.69%	0.63%	0.24%	0.01%
Colorectal cancer	4.83%	4.7%	1.98%	1.57%
Endometrial cancer	2.67%	2.1%	0.55%	0.41%

Lifetime incidence estimates—which in both our model and DevCan are based on the same age- and race-specific incidences and competing risks—are quite similar, providing some validation of the estimates of relative risk conditional on OC use used in the model and our underlying structural assumptions. The model-derived mortality estimates, which are independent of OC use and are based on age- and race-specific (black/white only) conditional survivals, are consistently lower than the DevCan estimates, which are derived from death certificate data. This is consistent with other “incidence-based mortality” models, where overall mortality estimates are derived from specific survival functions based on patient or tumor characteristics.<sup>5,6</sup> There are multiple possible explanations for this, including (1) the effect of competing risks for other cause mortality within the model after diagnosis, (2) age/period/cohort effects in the death certificate data that are not reflected in the model estimates, (3) the fact that SEER incidence and survival data represent a sample of the population, while the mortality data are derived from the entire population, and (4) inadequate modeling of mortality more than 5 years after survival (particularly for breast cancer). Since the potential underestimation of mortality affects both potential harms of OC use (breast and cervical cancer) and benefits (ovarian, endometrial, colorectal), the net effect on the overall balance of mortality harm and benefit is unclear—but is clearly worthy of further exploration.

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